A STUDY ON CORRELATION BETWEEN SERUM VITAMIN-D AND ESSENTIAL HYPERTENSION

DISSERTATION SUBMITTED FOR

M.D DEGREE (BRANCH – I)

GENERAL MEDICINE

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2012

CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON CORRELATION BETWEEN SERUM VITAMIN-D AND ESSENTIAL HYPERTENSION"** is the bonafide work of **Dr. S.KRISHNASAMY PRASAD,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2012.

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I, **Dr.S.KRISHNASAMY PRASAD,** solemnly declare that, I carried out this dissertation **"A STUDY ON CORRELATION BETWEEN SERUM VITAMIN-D AND ESSENTIAL HYPERTENSION"** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr.V.T.PREMKUMAR M.D** Professor, Department of General Medicine, Madurai Medical college, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch-I; examination to be held in April 2012.

Place: Madurai

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ACKNOWLEDGEMENT

I would like to thank **Dr.EDWIN JOE, M.D.,** Dean, Madurai Medical College,for permitting me to utilise the hospital facilities for the dissertation.

I also extend my sincere thanks to **Prof.Dr.MOSES .K.DANIEL M.D,**Head of the Department and Professor of Medicine for his constant support during the study.

I would like to express my deep sense of gratitude and thanks to my Unit Chief and Professor of Medicine, **Dr.V.T.PREMKUMAR M.D.,**for his valuable suggestions and excellent guidance during the study.

I thank the Assistant Professors of my Unit **Dr.K.S.MANIAPPAN M.D,** and **Dr.M.SOORIYAKUMAR, M.D.,** for their valid comments and suggestions.

Finally, I thank the patients for their extreme patience and co-operation

CONTENTS

Introduction

Vitamin D insufficiency affects almost 50% of the population worldwide[1]. This pandemic of hypovitaminosis D can mainly be attributed to lifestyle and environmental factors that reduce exposure to sunlight, which is required for ultraviolet-B (UVB)-induced vitamin D production in the skin. Levels of UVB radiation diminish with increasing distance from the earth's equator, during the winter months, and as a result of air pollution. Black people absorb more UVB in the melanin of their skin than do white people and, therefore, require more sun exposure to produce same amounts of vitamin D[2.] Importantly, conditions associated with reduced UVB-induced vitamin D production, such as high latitude, industrialization, and dark skin, have all been associated with increased blood pressure values[2]. The logical hypothesis that high UVB-induced vitamin D production is associated with low blood pressure was confirmed by a small trial of 18 patients with untreated essential hypertension[3]. The researchers found that systolic and diastolic blood pressure values were reduced by 6 mmHg after 6 weeks of UVB irradiation three times per week. UVB irradiation was also associated with a 162% rise in plasma 25-hydroxyvitamin D (25[OH]D) concentrations, but in hypertensive patients who received UVA irradiation, no significant change in 25(OH)D levels or blood pressure occurred[3].

The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population[4]. A meta-analysis published in 2007 showed that vitamin D supplementation was associated with significantly reduced mortality.[5] Furthermore, vitamin D insufficiency is associated with an increased risk of cardiovascular events, but whether this association reflects a causal relationship remains unclear[6, 7, 8]. The effect of vitamin D on blood pressure could be one of the potential mechanisms underlying the link between vitamin D and cardiovascular disease. In this Review, we will summarize the mechanisms that are presumed to underlie the relationship between vitamin D and arterial hypertension, and examine the clinical data for this association.

Review of literature

Hypertension

Elevated arterial blood pressure is a major cause of premature vascular disease leading to cerebrovascular events, ischaemic heart disease and peripheral vascular disease. Blood pressure is a characteristic of each individual, like height and weight, with marked interindividual variation, and has a continuous (bell-shaped) distribution. The levels of blood pressure observed depend on the characteristics of the population studied , in particular, the age and ethnic background.

Definition:

Hypertension is defined as elevated arterial pressure that place patients at increased risk for target organ damage. According to JNC-VII report hypertension is defined as one of the following; systolic blood pressure >140 mmHg; diastolic blood pressure >90 mmHg and those taking antihypertensive medications.

Cardiac output and peripheral resistance are the two determinants of arterial pressure. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and

anatomic changes in small arteries (lumen diameter 100–400 μm) and arterioles[9].

Classification:

This classification equates with those of the European Society of Hypertension and the World Health Organization-International Society of Hypertension [10].

Table: 1

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	< 120	< 80
Normal	< 130	< 85
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	≥180	≥110
Isolated systolic hypertension		
Grade 1	140-159	< 90
Grade 2	≥160	< 90

Prevalence:

Mohan *et al* reported an age-adjusted prevalence of 14% in Chennai. Gupta *et al* reported its prevalence in 36% men and 37% women in Jaipur

Diagnosis	**Percentage**
Essential hypertension	>95%
Renal hypertension	
Parenchymal	2-3%
Renovascular	1-2%
Endocrine hypertension	
Primary aldosteronism	0.3%
Cushings syndrome	<0.1%
Pheochromocytoma	<0.1%
OCP induced	2-3%
Miscellaneous	
Coarctation of aorta, PAN, neurogenic and drug induced	1%

The onset is usually between ages 25 and 55 years, it is uncommon before age 20 years. No specific cause is known for >95% of hypertension and the condition is known as essential hypertension. Secondary hypertension constitutes only 2-5% of cases.

Mechanism of hypertension:

Intravascular Volume

Vascular volume is a primary determinant of arterial pressure over the long term. Although the extracellular fluid space is composed of vascular and interstitial spaces, in general, alterations in total extracellular fluid volume are associated with proportional changes of blood volume. Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume initially expands and cardiac output increases. However, many vascular beds (including kidney and brain) have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase.

The initial elevation of blood pressure in response to vascular volume expansion is related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. The effect of sodium on blood pressure is related to the provision of sodium with chloride; non-chloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this "pressure-natriuresis" phenomenon may involve a subtle increase of glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases of arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due to

- A decrease in the filtration surface by a congenital or acquired deficiency in nephron number or function[11].
- A resetting of pressure-natriuresis relatonship[12].
- An acquired inhibitor of the sodium pumps.

- Nephron heterogenecity-presence of a sub group of nephrons that is ischemic either from afferent arteriolar vasoconstriction or from an intrinsic narrowing of the lumen.

Autonomic Nervous System

The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume, and chemoreceptor signals. Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. The three endogenous catecholamines are norepinephrine, epinephrine, and dopamine. All three play important roles in tonic and phasic cardiovascular regulation.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings located in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease of sympathetic outflow, resulting in decreases of arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial

pressure that may occur during postural changes, behavioural or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases of arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes.

Pheochromocytoma is the most obvious example of hypertension related to increased catecholamine production, in this instance by a tumour. Blood pressure can be reduced by surgical excision of the tumour or by pharmacologic treatment with an α_1 receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. Increased sympathetic activity may contribute to other forms of hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although perhaps not a causative, role in the maintenance of increased arterial pressure.

Renin-Angiotensin-Aldosterone:

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II

and the sodium-retaining properties of aldosterone. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the thick ascending limb of the loop of Henle (macula densa mechanism), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via β_1 adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by β_1 receptor blockade. In addition, renin secretion may be modulated by a number of humoral factors, including angiotensin II. Angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either ACE or angiotensin II receptors.

The sequence of changes in patients with renovascular hypertension starts with the release of increased amounts of renin when sufficient ischemia is induced to diminish pulse pressure against the juxtaglomerular cells in the renal afferent arterioles. A reduction in renal perfusion pressure by 50 percent leads to an immediate and persistent increase in renin secretion from the ischemic kidney, along with suppression of secretion from the contralateral one. With time, an expanded body fluid volume causes renin levels to fall but not to the low level expected from the elevated BP[13].

VASCULAR:

Radius and compliance of resistance arteries are also important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce lumen diameter of small arteries and arterioles. Remodelling refers to geometric alterations in the vessel wall without changing vessel volume.

Hypertensive patients have stiffer arteries, and arteriosclerotic patients may have particularly high systolic blood pressures and wide pulse pressures as a consequence of decreased vascular compliance due to structural changes in the vascular wall. Recent evidence suggests that arterial stiffness has independent predictive value for cardiovascular events.

Endothelial dysfunction:

Endothelium is now known to be the source of multiple relaxing and contracting substance of which nitric oxide is an important vasodilator. hypertensive patients have been shown to have impaired nitric oxide mediated vasodilatory response.

Hyperinsulinemia / insulin resistance:

An association between hypertension and hyperinsulinemia has been established not only in obese but also non obese hypertensive. The hyperinsulinemia of hypertension arises as a consequence of resistance to the effects of insulin on peripheral glucose utilization. Insulin has multiple pressor effects, including activation of sympathetic activity, trophic action on vascular hypertrophy and increased renal sodium absorption. Normally the pressor effects are counteracted by insulin mediated increased synthesis of nitric oxide leading to normalisation of pressor effect.

Essential Hypertension

Essential hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of essential hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is likely that essential hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have a volume-dependent hypertension. Inconsistent associations between plasma aldosterone and blood pressure have been described in patients with essential hypertension. The association between aldosterone and blood pressure is more striking in African Americans, and PRA tends to be low in hypertensive African Americans. This raises the possibility that subtle increases of aldosterone may contribute to hypertension in at least some groups of patients who do not have overt primary aldosteronism. Furthermore, spironolactone, an aldosterone antagonist, may be a particularly effective antihypertensive agent for some patients with essential hypertension, including some patients with "drug-resistant" hypertension.

Pathologic Consequences of Hypertension:

Hypertension is a risk factor for all clinical manifestations of atherosclerosis. It is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD).

Heart

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, diastolic dysfunction, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias.

Both genetic and hemodynamic factors contribute to left ventricular hypertrophy. Clinically, left ventricular hypertrophy can be diagnosed by electrocardiogram, although echocardiography provides a more sensitive measure of left ventricular wall thickness. Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. It is not clear if different classes of antihypertensive agents have an added impact on reducing left ventricular mass, independent of their blood pressure–lowering effect.

Brain

Hypertension is an important risk factor for brain infarction and haemorrhage. Approximately 85% of strokes are due to infarction and the remainder are due to haemorrhage, either intracerebral haemorrhage or

subarachnoid haemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years. Treatment of hypertension convincingly decreases the incidence of both ischemic and hemorrhagic strokes.

Kidney

Primary renal disease is the most common etiology of secondary hypertension. Conversely, hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the entire distribution of blood pressure above optimal. The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Peripheral Arteries

In addition to contributing to the pathogenesis of hypertension, blood vessels may be a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index < 0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. Several studies suggest that an ankle-brachial index < 0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

VITAMIN D

Vitamin D is the name of a group fat-soluble compounds that are essential for maintaining the appropriate mineral balance in the body. Vitamin D, called the most important vitamin, was discovered 1922 and at the time was primarily associated with bone health. The chemical structures of the D vitamins were determined in the 1930s by Professor Adolf Windaus's

laboratory at the University of Göttingen in Germany and in 1971 Anthony W. Norman at the University of California, discovered the 1,25-dihydroxyvitamin D, the active form of vitamin D hormone.

Vitamin D belongs to a group of several related sterols, with the two most important being D2 (ergocalciferol) and D3 (cholecalciferol) (Figure 1). The two forms differ chemically only in their side-chain structure, vitamin D2 has a side chain that contains a double bond between carbon 22 and carbon 23 and a carbon 24 methyl group[14,15].

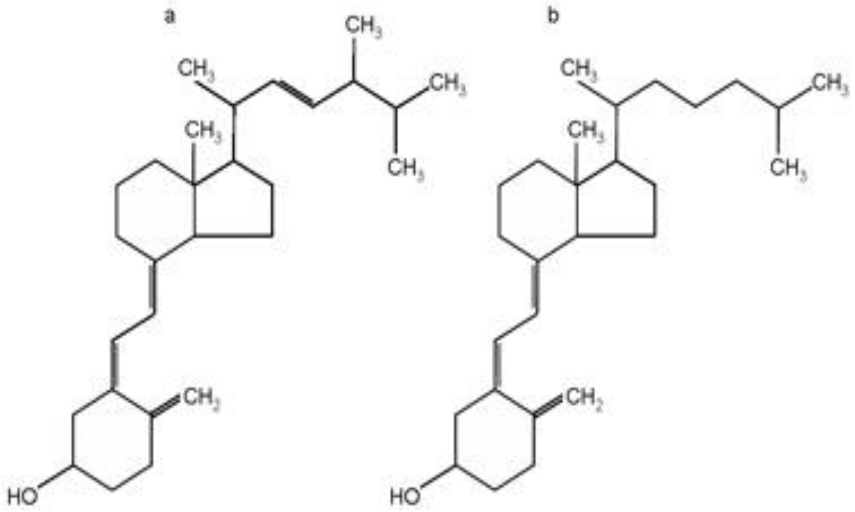


Figure 1.

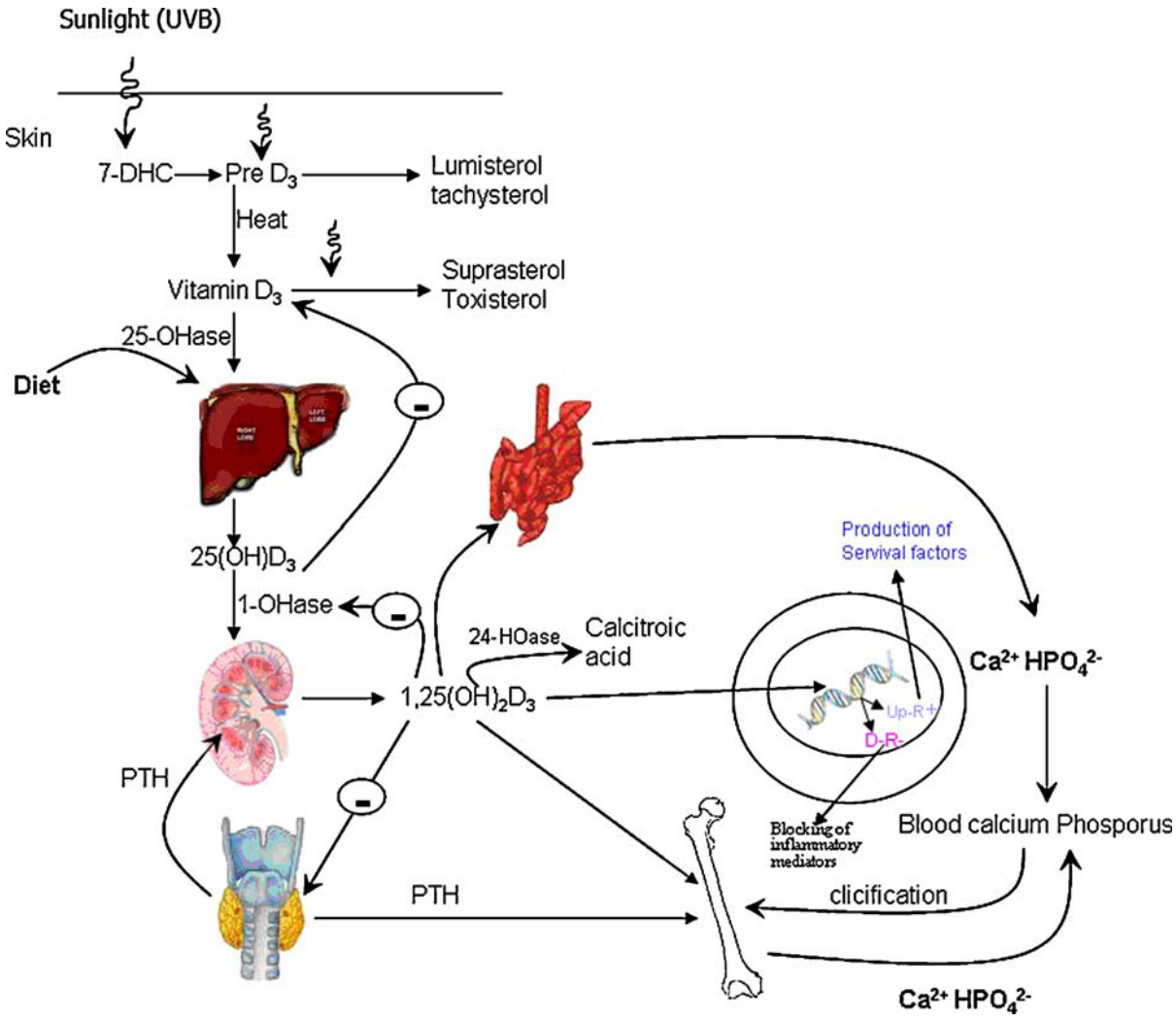
a) D2 (ergocalciferol)

b) D3 (cholecalciferol)

UVB-INDUCED VITAMIN D

SUNLIGHT EXPOSURE

Sunlight is composed of radiation of varying wavelengths, ranging from the infrared long wavelength light to the ultraviolet short wavelength light (UV). UV light is further divided into UVA (315 nm-400 nm) and the shorter wavelength UVB radiation. UVB causes sunburns, but it also initiates Vitamin-D production in the skin. The 7-dehydrocholesterol (pro-vitamin D), a cutaneous membrane lipid, absorbs UVB radiation between wavelengths of 280 and 315 nm and will thereby be converted into pre-vitamin D3 (pre-cholecalciferol). Pre-vitamin D3 will isomerize into vitamin D3 (cholecalciferol) . Vitamin D3 is transported to the liver by binding to VDBP. In elderly, the production capacity of vitamin D is lowered because of atrophy of the skin due to lower amount of membrane lipids [16].



SKIN TYPE

Larger amounts of the pigment melanin in the epidermal layer result in darker skin and decrease the capacity of the skin to produce vitamin D from UVB radiation [17]. Reports consistently indicate lower circulating 25(OH)D levels in black persons compared with Caucasians. However it is not clear whether lower levels of 25(OH)D in persons with dark skin cause health concerns.

AGE

Elderly people in Europe, especially nursing home residents, often suffer from vitamin D insufficiency. Aging decreases the amount of 7-dehydrocholesterol produced in the skin by as much as 75% by the age of 70 years. Therefore, a 70 year old person has approximately 25% of the capacity to produce cholecalciferol compared with a healthy young adult [18]. However the skin has such a large capacity to make vitamin D that even elderly exposed to sunlight can achieve increased circulating concentrations of 25(OH)D.

OBESITY

Obese individuals have been shown to have low circulating 25(OH)D concentrations [19,20]. Since vitamin D is a fat soluble vitamin and is readily stored in adipose tissue, it could be sequestered in the larger body pool of fat of obese individuals. Researchers have observed that circulating 25(OH)D concentrations increased in both obese and lean subjects after exposure to an identical quantity of UVB radiation[21]. Obese subjects has a larger body surface area of exposure and would be expected to produce more pre-vitamin D which would result in higher circulating 25(OH)D concentrations, than would the lean subjects.

However, the increase was less than half in the obese subjects than in the lean, one day after exposure. This indicates that the subcutaneous fat, which stores vitamin D, sequestered more of the cutaneous synthesized vitamin D in the obese than in the lean subjects since there was more fat available for this process. It has been suggested that obese individuals may avoid exposure to solar UV radiation, which is crucial for the cutaneous synthesis of vitamin[22].

SOURCES

Vitamin D is unique because it is derived from sunlight and foods. Vitamin D occurs only in foods of animal origin. Liver, egg yolk, butter, and cheese, and some species of fish contain useful amounts. Fish liver oils although not considered to be a food are the richest source of vitamin D. Human milk has recently been shown to contain considerable amounts of water soluble vitamin D sulphate . Other sources of vitamin D are foods artificially fortified with vitamin D, such as milk, margarine, vanaspathi, and infant foods[23].

DIETARY SOURCES OF VITAMIN D

	µg/per 100g		µg/per 100g
BUTTER	0.5-1.5	SHARK LIVER OIL	30-100
EGGS	1.25-1.5	COD LIVER OIL	200-750
MILK	0.1	HALIBUT LIVER OIL	500-10,000
FISH FAT	5-30		

GENETIC FACTORS

Worldwide variations observed in circulating 25(OH)D concentrations may be due to common environmental factors such as UVB exposure dependent on latitude, season, clothing related to religious or cultural issues, as well as diet, and fortified-food strategies. Individual behavioural aspects such as clothing, use of sunscreen, time spent outdoors, sun habits, use of vitamin D supplements, skin sensitivity and the body fatness may also affect concentrations [24,25,26]. Individual and environmental factors as well as genetic predisposition could play a role in the possibility to increase circulating 25(OH)D levels. It is very important to further investigate the influence of genetic factors as compared with environmental factors on the vitamin D status. There are conflicting results regarding the genetic effect on summer and winter vitamin D status[27,28]. Vitamin D concentrations could be influenced by genetic factors in several potential ways. First is individual skin sensitivity and the capacity to produce vitamin D3, which includes the presence of the substrate 7-dehydrocholesterol, the ability to convert 7-dehydrocholesterol to pre-vitamin D3 and further to vitamin D3. Second is the catabolism of formed pre-vitamin D3 into inactive vitamin D photoproducts such as lumisterol, tachysterol, suprasterols, and toxisterols. Third alternative genetic factor that may influence circulating 25(OH)D concentrations involves the vitamin D-binding protein (VDBP), which binds to vitamin D and its plasma metabolites and transports

them to target tissue[29,30]. Another process possibly influenced by genes is the hydroxylation of 25(OH)D to 1,25(OH)D by the enzyme 1,α-hydroxylase, particularly since 1,α-hydroxylase has been found in almost all cells and tissues [31,32].

THE ROLE OF VITAMIN D IN HEALTH

In epidemiological studies vitamin D has been suggested to prevent several diseases. While it may not be a cure, a deficiency in vitamin D may be a risk factor for disease and therefore the increase in the number of individuals being diagnosed with vitamin D deficiency can be a public health problem.

BONE HEALTH

The steroid hormone 1,25(OH)D gets transported by the VDBP to its target organs which control calcium and phosphorus metabolism. The interaction between 1,25(OH)D and its nuclear vitamin D receptor (VDR) in the small intestine increases the expression of calcium channels and calcium binding protein which results in increased absorption of calcium from the diet [33,34]. Vitamin D sufficiency will activate the calcium transport system and permits dietary calcium to be absorbed into the bloodstream. A low dietary intake of calcium will increase the secretion of parathyroid hormone (PTH), which improves renal production of 1,25(OH)D, thereby increasing the efficiency of calcium absorption. 1,25(OH)D will also increase the absorption

of dietary phosphorus. Approximately 55–70% of dietary phosphorus is passively absorbed. Vitamin D increases phosphorus absorption by an additional 20% so that approximately 80% of dietary phosphorus is absorbed . The main function of vitamin D is to uphold serum calcium within a satisfactory range for the maintenance of neuromuscular function, signal transduction and a wide variety of metabolic processes[35]. In infants and children, heavy vitamin D deficiency results in failure of bone mineralization. Rapidly growing bones are at the greatest risk to be affected by rickets. The growth plates of bones continue to broaden, but in the absence of satisfactory mineralization, arms and legs become deformed. In infants, the result of rickets might be delayed closure of the fontanels in the skull, and the rib cage may become deformed because of the pulling action of the diaphragm. Although vitamin D fortification of foods has led to decrease in vitamin D deficiency in most developed countries, nutritional rickets is still being described in places all over the world [36,37]. Adult bones that are no longer growing are still in a constant state of turnover, or "remodelling". The collagenous bone matrix is maintained but bone mineral is gradually lost, causing bone pain and osteomalacia (soft bones) in adults with severe vitamin D deficiency. Although osteoporosis is a multifactorial disease, vitamin D insufficiency can be a very important contributing factor.

CANCER

Two characteristics of cancer cells are the lack of cell differentiation and rapid uncontrolled growth or proliferation. Most malignant tumors, including breast, lung, skin, colon, and bone tumors, have been discovered to contain VDR. The biologically active form of vitamin D, 1,25(OH)D and its analogs, have been found to induce cell differentiation and suppress proliferation of a number of cancerous and noncancerous cell types preserved in cell culture[38]. The worldwide distribution of for example colon cancer mortality shows a similar pattern as the historical geographic distribution of rickets[39,40], providing some evidence that low sunlight exposure and vitamin D status might be related to an increased risk of colon cancer. More recent studies have reported that greater vitamin D intakes and circulating 25(OH)D concentrations are associated with decreased colorectal cancer risk. A five-year prospective study with more than 120 000 participants, reported that men with the highest vitamin D intake had a 29% decreased risk of colorectal cancer compared to men with the lowest vitamin D intakes [41]. Another study with pooled, dose-response analysis of two case-control studies showed that women with breast cancer had significantly lower circulating 25(OH)D concentrations compared to the controls [42,43]. Another study reported that women with circulating 25(OH)D concentration of ~130 nmol/L (52 ng/ml) had a 50% lower risk of developing breast cancer compared to women with 25(OH) D levels lower than 32.5 nmol/L (13 ng/mL) . In a prospective study from Finland, Norway and Sweden,

a U-shaped relationship between serum 25(OH) D levels and prostate cancer risk was observed; circulating 25(OH)D concentrations of 19 nmol/L (7.6 ng/ml) or lower and 80 nmol/L (32 ng/ml) or higher were associated with higher prostate cancer risk [44]. Epidemiological studies have demonstrated an association between risk factors for prostate cancer and environmental conditions that can result in low vitamin D levels . There is a higher incidence of prostate cancer in African American men than in white American men, and the higher amount of melanin content in dark skin is known to reduce the efficiency of vitamin D synthesis [45].

AUTOIMMUNE DISEASES

Data from human, animal, and in vitro experiments are suggesting that vitamin D might play an important part in the autoimmunity [46]. There is accumulating evidence of vitamin D status as a potential environmental factor affecting autoimmune disease prevalence. An unhealthy vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis (MS) [47], rheumatoid arthritis (RA) [48], diabetes mellitus (DM) [49], and inflammatory bowel disease (IBD) . It is clear that both genetic and environmental factors affect the prevalence of above mentioned diseases. Vitamin D has been involved as a factor in many different autoimmune diseases which suggest that vitamin D might be an environmental factor that normally

participates in the control of the “self-tolerance” where the body does not mount an immune response to self-antigens. In addition, there may be a greater vitamin D requirement for patients at risk for developing or already having an autoimmune disease. The ideal amount of vitamin D to support the immune system may be different from the amount of vitamin D that is required for prevention of other diseases or to maintain calcium homeostasis . In addition to the data that indicate vitamin D status as an environmental factor that affects autoimmune disease prevalence, patients with autoimmune diseases also have been shown to express genetic polymorphisms for vitamin D regulatory genes. Polymorphisms in the VDR have been associated with increased susceptibility to MS [50], RA[51], Dm[52] and IBD [53].

Cardiovascular diseases

The etiology of cardiovascular diseases (CVD) is still not totally understood. Mounting evidence suggests that vitamin D deficiency is associated with increased risk of cardiovascular diseases, but the underlying mechanisms remain to be explored in detail[54] . Data from epidemiologic studies indicate that geographic latitude, altitude, season, and the place of living are all associated with CVD mortality[55]. There have been no adequate explanations offered for these coincidences. However, these environmental factors all share the property of influencing UVB exposure and therefore also human vitamin D status. The

vitamin D hypothesis regarding the etiology of CVD is in line with the higher prevalence of CVD in obese and elderly individuals and the low prevalence of CVD in physically active individuals, since vitamin D status is inversely associated to body weight [56] and age[57, 58] and is positively associated to the level of physical activity . Also ethnicity influence vitamin D status and CVD risk [59]. A systematic review show a statistically significantly inverse association between circulating 25(OH)D concentrations and cardiovascular disease among nine prospective studies regarding both CVD incidence and mortality, however there was a heterogeneity among the studies .

There are a number of mechanisms that might clarify the association between vitamin D status and CVD, among them an association of vitamin D with inflammatory markers. Activity of 1α-hydroxylase is regulated by several inflammatory and hormonal mechanisms which suppresses 1α-hydroxylase activity . 1α-hydroxylation of 25(OH)D occur in most cells and tissues in the body, nevertheless circulating concentrations of 1,25(OH)D are mainly predicted by renal 1α-hydroxylase activity. The VDR is nearly ubiquitously expressed, and almost all cells respond to 1,25(OH)D exposure; about 5% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system . This suggests a widespread function and possible causal relationship between vitamin D deficiency and cardiovascular risk.

VITAMIN D AND BLOOD PRESSURE

MECHANISMS

THE RENIN-ANGIOTENSIN SYSTEM (RAS)

Vitamin D is a negative regulator of the hormone renin, the essential hormone of the RAS[60]. Increased activation of the RAS, which is a main regulator of electrolyte and volume homeostasis, contributes to the development of arterial hypertension [61]. Mechanistic insights have been gained by studying mice deficient for the vitamin D receptor, which develop hypertension and adverse cardiac remodelling mediated via the renin-angiotensin system [62]. Increased activation of the renin–angiotensin–aldosterone system (RAAS), which is a main regulator of electrolyte and volume homeostasis, contributes to the development of arterial hypertension. Renin is mainly synthesized by the juxtaglomerular cells of the kidney and stimulates the production of angiotensin II and of aldosterone, which increase blood pressure directly by vasoconstriction and indirectly by salt and water retention and other mechanisms. Inappropriate, increased activation of the RAAS has been reported in VDR and 1α-hydroxylase knockout mice, although it should be acknowledged that the increase in renin activity did not achieve statistical significance. Importantly, VDR and 1α-hydroxylase knockout mice developed arterial hypertension and myocardial hypertrophy, which were present even after normalization of calcium homeostasis; however, blocking of the RAAS

system with angiotensin-converting-enzyme inhibitors normalized blood pressure and cardiac abnormalities, Furthermore, increased RAAS activation, arterial hypertension, and myocardial abnormalities could be successfully treated with 1,25(OH)2D in 1α-hydroxylase knockout mice. The molecular effects of vitamin D on the RAAS have been clarified by the finding that liganded VDR suppresses renin expression by binding to the transcription factor cAMP-response element-binding protein (CREB). As a result, stimulation of renin transcription is inhibited because CREB is no longer able to stimulate renin transcription by binding to cAMP response elements in the promoter region of the renin gene. In patients with arterial hypertension, renin activity has been inversely associated with 1,25(OH)2D levels.

EFFECTS ON CELLS OF THE VESSEL WALL

Vitamin D and its equivalents cause several effects on the cells of the vessel wall, which include vascular smooth muscle cells, endothelial cells and macrophages, all of them expressing the VDR as well as 1α-hydroxylase[25]. Vitamin D's effect on vascular smooth muscle cells is complex and is also modulated by other hormones, such as parathyroid hormone and estrogenic compounds, which up-regulate 1α-hydroxylase in these cells[63]. 1,25(OH)D is thought to protect against vascular problems by decreasing endothelial adherence molecules, by increasing the activity of endothelial nitric oxide synthase, and through its anti-inflammatory properties[64].

AIMS AND OBJECTIVES

1. To study the level of vitamin- D in patients with essential hypertension.

2. To identify whether any association exists between age , sex, body mass index, diabetes, and target organ damage and the presence of decreased level of vitamin -D.

MATERIALS AND METHODS

Setting	Government Rajaji hospital and Madurai medical college, Madurai.
Collaborative department	Department of biochemistry, Madurai medical college, Madurai.
Study design	Cross sectional study
Period of study	1-4-2011 to 30-09-2011.
Sample size	40 cases and 20 controls
Ethical committee approval	The present project was approved by the ethical committee
Conflict of interest Financial support	Nil Nil

INCLUSION CRITERIA:

- Patients with essential hypertension
- Patients whose age were above 25 years,
- Both sexes were included.

EXCLUSION CRITERIA:

- Individuals below 25 years were excluded
- Patients with renal failure
- Pregnancy
- Patients with secondary hypertension
- Patients who were on calcium or vitamin –D supplements
- Patients on long term diuretics.
- Patients receiving any other vitamin D supplementation.

CONTROLS:

Subjects whose age were above 25 years and had normal blood pressure and who met the above exclusion criteria.

Consent

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing

participants were taken up after getting a written informed consent from them.

Materials

Around 40 cases and 20 controls meeting the above said criteria and who gave written informed consent were taken as subjects for the study.

LIMITATIONS

1. In this study, both newly detected as well as known cases of essential hypertension on treatment were included in the study.
2. The study population included patients with essential hypertension both with and without target organ damage and other cardiovascular risk factor but without renal failure.
3. The study was only an observational study of hypovitaminosis-d in hypertensive patients and controls were included.

METHODS

Selected socio-demographic, clinical and laboratory data were elicited from the patients and recorded in a profoma . (annexure – I)

I. SOCIO-DEMOGRAPHIC DATA

- Age
- Sex

II. CLINICAL DATA

- Body mass index
- Systolic and diastolic blood pressure
- Cardiovascular risk factors
- Clinical examination

III. LABORATORY DATA

- Blood urea : Estimation done manually by using diacetyl monoxime technique
- Serum Creatinine : Estimation was done using COBAS autoanalyser.
- Serum albumin : Bromo cresol green (end point assay)
- Serum calcium : Arsenazo III method.

- Serum phosphorus : UV Molybdate (end point assay).
- Serum uric acid : Acid enzymatic method.
- Vitamin D : Enzyme immune assay

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Definitions used in the present study

- **Essential hypertension**

  According to the JNC-VII report , hypertension is defined as systolic blood pressure of 140mm Hg and above and or diastolic blood pressure of 90mmHg and above . In newly detected cases it was the mean of 3 relaxed , seated right arm reading. The diagnosis that the hypertension is essential and not secondary was made on the over all clinical impression only. Laboratory investigations to rule out secondary causes were not done in each case .

- **HYPOVITAMINOSIS –D**

  Hypovitaminosis-D is defined in this study as serum level of Vitamin – D less than 37.5nmol/l

- **DIABETES MELLITUS**
  - Already a known case of diabetes mellitus on treatment
  - Fasting plasma glucose > 126m g/dl
  - Two hour plasma glucose > 200mg/dl
  - Symptoms of diabetes plus random blood glucose > 200mg/dl
- **LEFT VENTRICULAR HYPERTROPHY**

  Based on electrocardiographic findings satisfying either sokolon-lyon criteria or cornell voltage criteria .

- **HYPERTENSIVE RETINOPATHY**

  Based on keith- wagner – baker grading

  Grade I – attenuation of arteries

  Grade II - arterio-venous nipping

  Grade III - with haemorrhage and exudates

  Grade IV – with papilledema.

RESULTS

A : PROFILE OF CASES STUDIED

TABLE 1: AGE DISTRIBUTION

Age group	**Normotensive group**		**Hypertensive group**	
	No	**%**	**No**	**%**
Upto 50 years	-	-	8	20
51-60 years	8	40	12	30
61-70 years	11	55	16	40
> 70 years	1	5	4	10
Total	20	100	40	100
Range	54-71 years		31-77 years	
Mean	63.0 years		59.0 years	
SD	5.5 years		9.6 years	
'p'	0.133 Not significant			

The hypertensive group had an age of 59 $\pm$9.6 years and the normotensive group 63 $\pm$5.5 years. There was no statistically significant difference.

AGE DISTRIBUTION

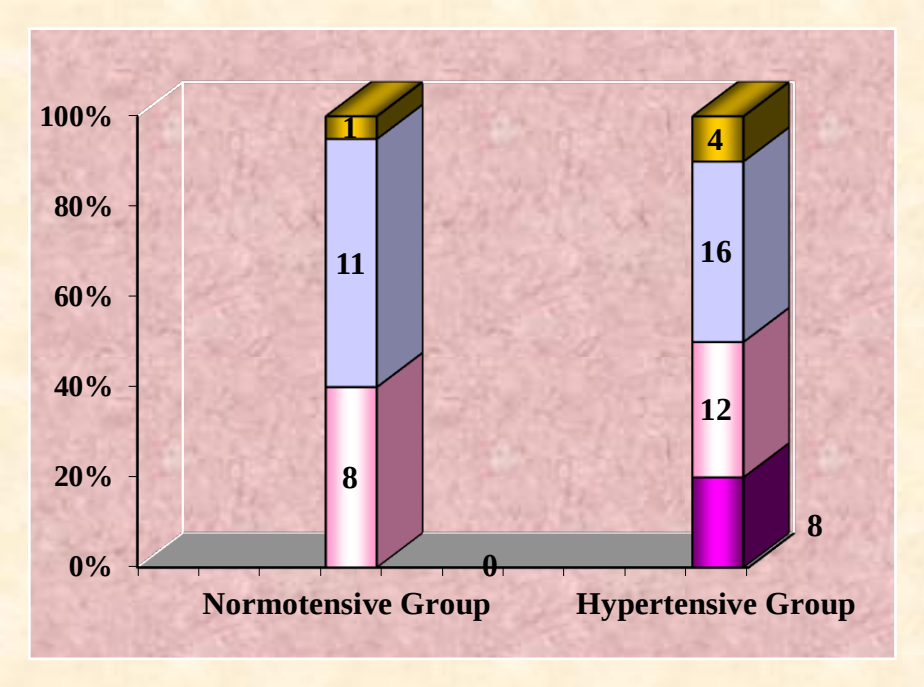


TABLE 2: SEX DISTRIBUTION

Sex	**Normotensive cases**		**Hypertensive Cases**	
	No	**%**	**No**	**%**
Male	14	70	29	72.5
Female	6	30	11	27.5
Total	20	100	40	100
'p'	0.9193 Not significant			

The control group had 20 patients of which 14 were male and 6 were female , and 40 hypertensive patients were included of which 29 were male and 11 were female. Sex distribution of the study group and control group did not have any significant difference (p = 0.9193).

SEX DISTRIBUTION

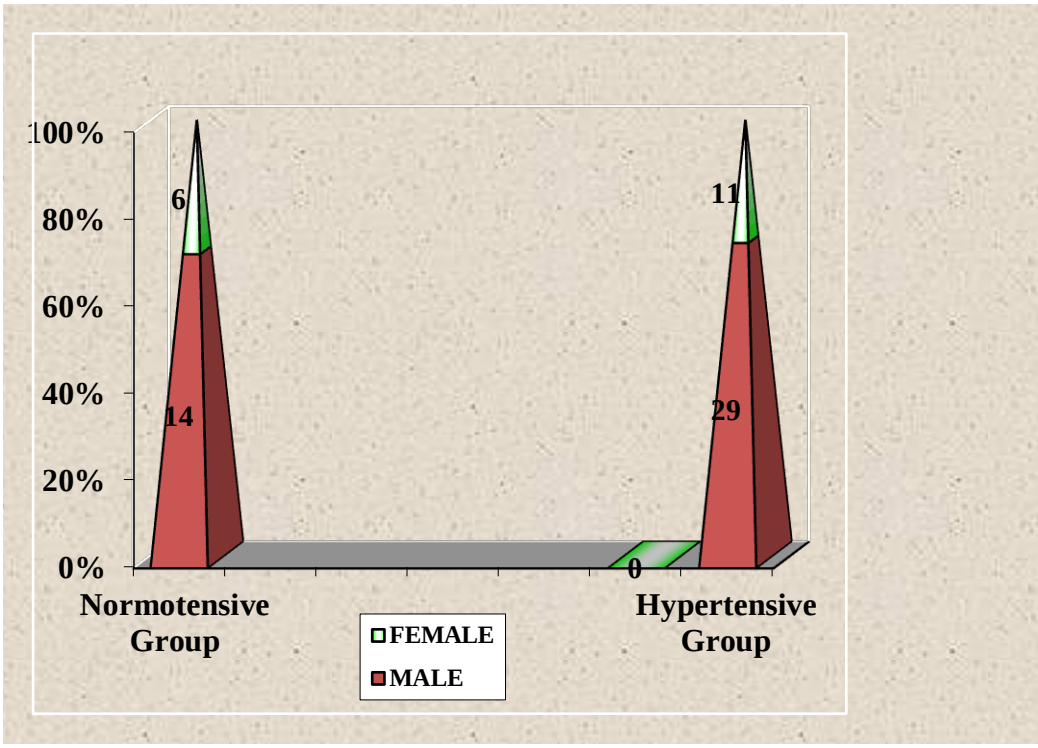


TABLE 3: PHYSIOLOGICAL VARIABLES

Variable	**Normotensive**		**Hypertensive**		**'p'**
	Mean	**SD**	**Mean**	**SD**	
Height (in cms)	166.1	5.9	163.1	6.4	0.1112 Not significant
Weight (in kgs)	70.3	7.7	65.9	8.5	0.1052 Not significant
BMI	25.46	2.81	25.1	3.07	0.672 Not significant

Height, weight and BMI of the normotensive and hypertensive cases studied did not have any significant difference ($p > 0.05$).

PHYSIOLOGICAL VARIABLES

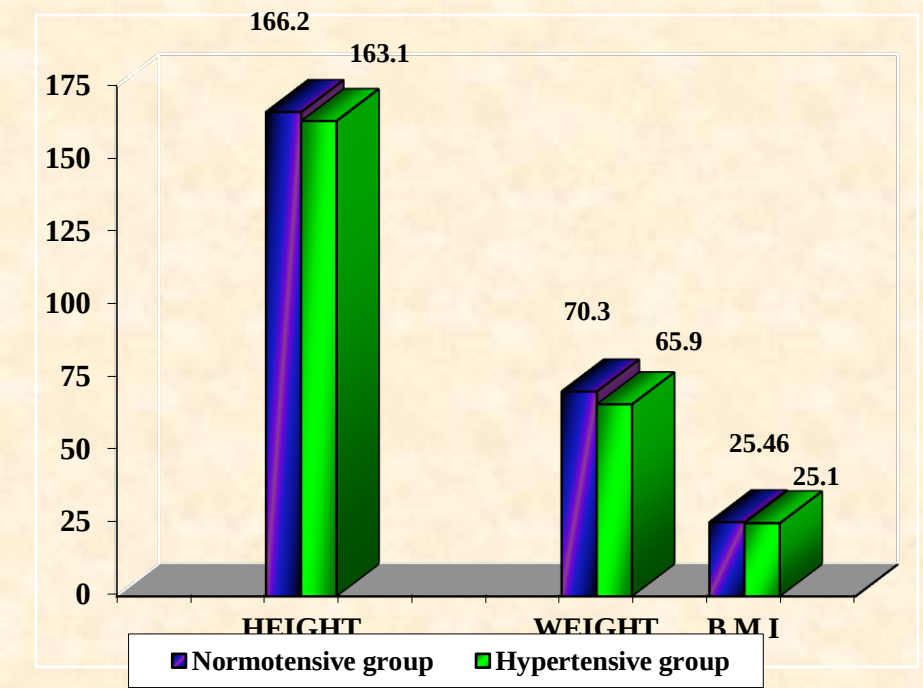


TABLE 4: BLOOD PRESSURE

Blood pressure	**Normotensive**		**Hypertensive**		**'p'**
	Mean	**SD**	**Mean**	**SD**	
SBP	115	5.91	163.05	16.7	**0.0001** **Significant**
DBP	75.0	5.1	95.95	9.33	**0.0001** **Significant**

Systolic and diastolic blood pressures of the normotensive groups (115 $\pm$ 5.91 and 75 $\pm$5.1) were significantly lower than those of the hypertensive group (163.05 ± 16.67and 95.95 $\pm$ 9.33).

BLOOD PRESSURE IN HYPERTENSIVE AND NORMOTENSIVE

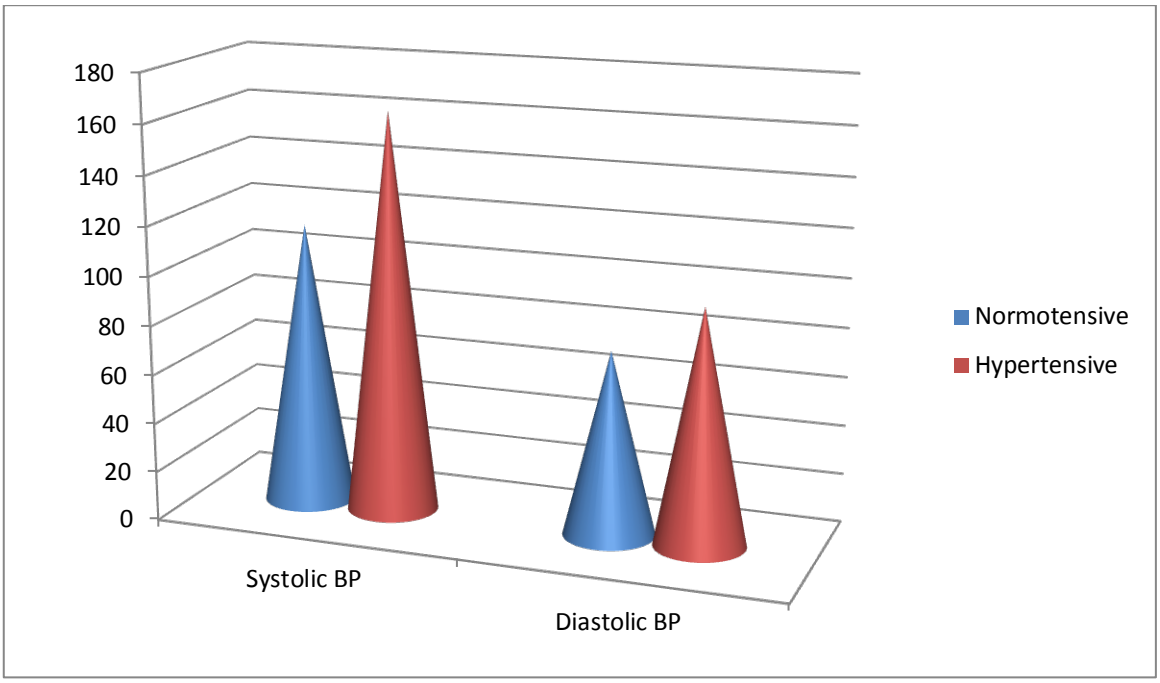


TABLE 5 : RISK FACTORS AND TARGET ORGAN DAMAGE

Factors	**Normotensive cases**		**Hypertensive Cases**		**'p'**
	No	**%**	**No**	**%**	
a) Smoking (among males)					
Yes	11	78.6	27	93.1	0.1858
No	3	21.4	2	6.9	Not significant
b) Echo					
Normal	20	100	21	52.5	**0.0006**
Abnormal	-	-	19	47.5	**Significant**
c) DM					
Yes	6	30	13	32.5	0.9218
No	14	70	27	67.5	Not significant
d) **Retinopathy**					
I	-	-	6	15	
II	-	-	8	20	
III	-	-	7	17.5	**0.0001**
IV	-	-	7	17.5	**Significant**
Total	Nil	Nil	28	70	
No	20	100	12	12	
e) ECG					
LAD	1	5	4	10	**0.0003**
LAD, LYH	-	-	19	47.5	**Significant**
WNL	19	95	17	42.5	

Percentage of abnormal values in Echo, ECG and Retinopathy were significantly higher in the hypertensive group ($p < 0.05$).

TARGET ORGAN DAMAGE

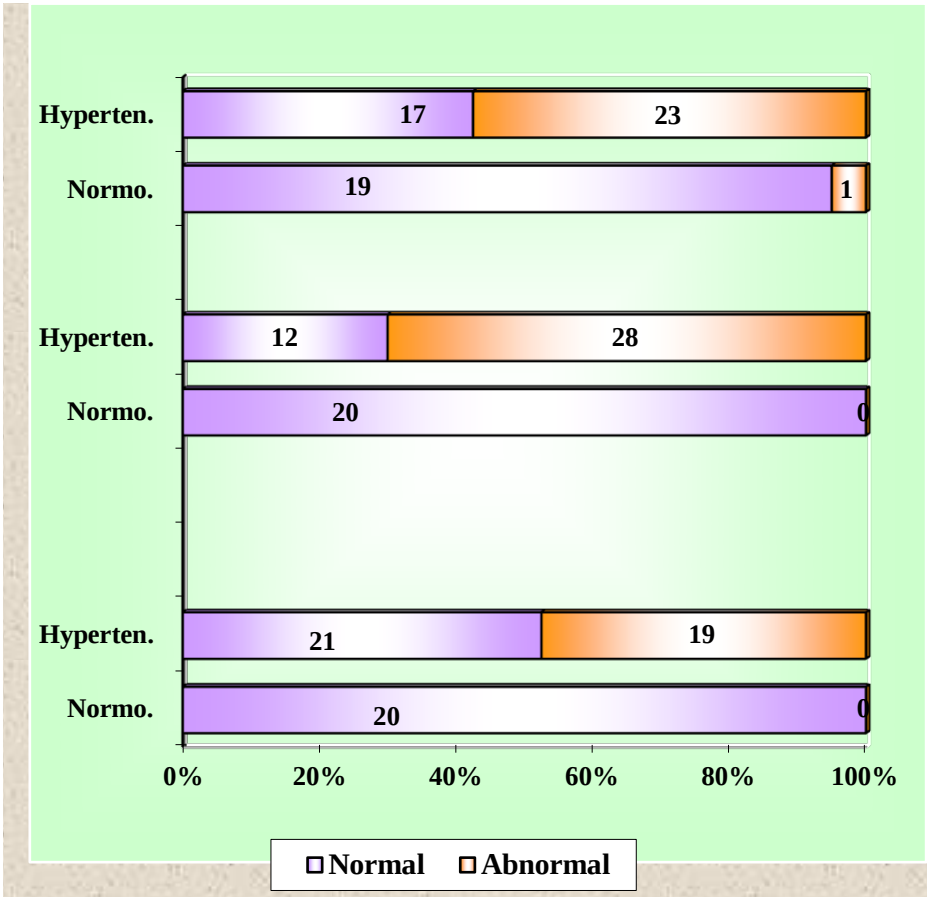
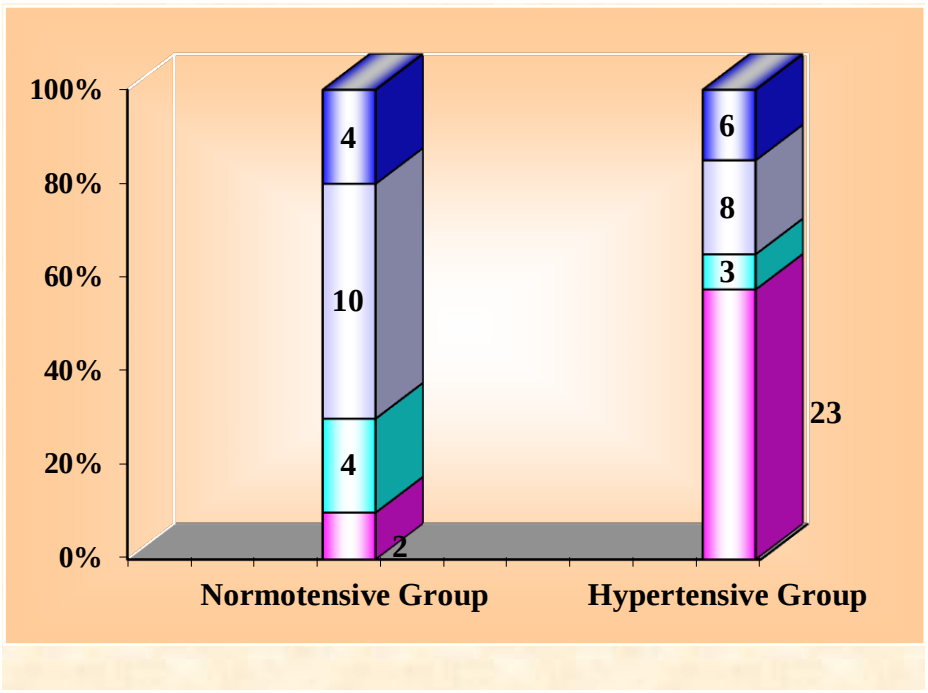


TABLE 6: VITAMIN D LEVELS

Vitamin D level	**Normotensive Cases**		**Hypertensive Cases**	
	No	**%**	**No**	**%**
Level – I - (< 37.5 nmol L^{-1})	2	10	23	57.5
Level II - (<37.5 – 49.9 nmol L^{-1})	4	20	3	7.5
Level III - (50 – 74.9 nmol L^{-1})	10	50	8	20.0
Level IV- (75 – 100 nmol L^{-1})	4	20	6	15.0
Vit D (in nmol L^{-1}) Range Mean SD	 24.9 – 90 62.3 18.4		 20.8-88.9 46.6 20.6	
P	**0.0072** **Significant**			

The mean Vit. D value in the normotensive cases was 62.3 nmol L^{-1}. This was significantly higher than their mean values in hypertensive cases (46.6 nmol L^{-1}). This difference was statistically significant (p = 0.0072).

VITAMIN-D LEVEL



B: RELATIONSHIP BETWEEN VIT D LEVELS AND OTHER VARIABLES IN HYPERTENSIVE CASES

TABLE 7: VIT D LEVELS AND AGE

Vit D	**Age in years**	
	Mean	**SD**
I	58.3	9.2
II	64.7	8.6
III	58.6	11.5
IV	59.5	10.7
'p'	0.7144 Not significant	

Vit D values and age of the patient did not have any statistically significant relationship (p = 0.7144).

TABLE 8: VIT D LEVEL AND SEX

Vit D level	**Sex**			
	Male (29)		**Female (11)**	
	No	**%**	**No**	**%**
I	17	58.6	6	54.5
II	2	6.9	1	9.1
III	6	20.7	2	18.2
IV	4	13.8	2	18.2
Vit D Range Mean SD	 20.8 – 88.9 45.7 21.5		 31.2 – 78.4 49.0 18.9	
'p'	0.2142 Not significant			

Vit D levels among males and females did not have any significant difference ($p > 0.05$).

TABLE 9: VIT D LEVEL AND PHYSIOLOGICAL PARAMETERS

Vit D level	**Height**		**Weight**		**BMI**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
I	162.3	6.6	67.6	8.5	25.69	2.99
II	159.7	5.7	63.3	12.7	24.68	3.17
III	163.1	7.2	6.3	5.8	23.77	2.8
IV	161.5	6.4	64.7	10.0	24.83	3.84
'p'	0.8982 Not significant		0.4115 Not significant		0.5131 Not Significant	

In the hypertensive cases, there was no significant relationship between Vit D levels and height, weight and BMI of the patients ($p > 0.05$).

TABLE 10:VITAMIN D LEVELS AND OTHER QUANTITATIVE PARAMETERS

Variable	**Value (Mean ±SD) for cases with Vit. D level**				**'p'**
	I	**II**	**III**	**IV**	
Urea	27.7 ±7.2	23.3 ±1.5	28.3 ±7.4	29 ±6.8	0.6582 Not significant
Corr. Ca	7.65 ±0.44	7.58 ±0.43	8.02 ±0.33	8.5 ±0.54	**0.0061** **Significant**
Phosphate	3.97 ±0.74	3.8 ±1.37	3.86 ±0.84	3.52 ±0.51	0.5447 Not significant
Albumin	3.51 ±0.43	3.73 ±0.25	3.55 ±0.31	3.4 ±0.22	0.4713 Not significant
Sr. Creatinine	1.2 ±0.23	1.07 ±0.21	1.16 ±0.14	1.13 ±0.12	0.7268 Not significant

There was significant association between Corr.Ca. and Vit. D levels in hypertensives

VIT. D LEVELS & CALCIUM

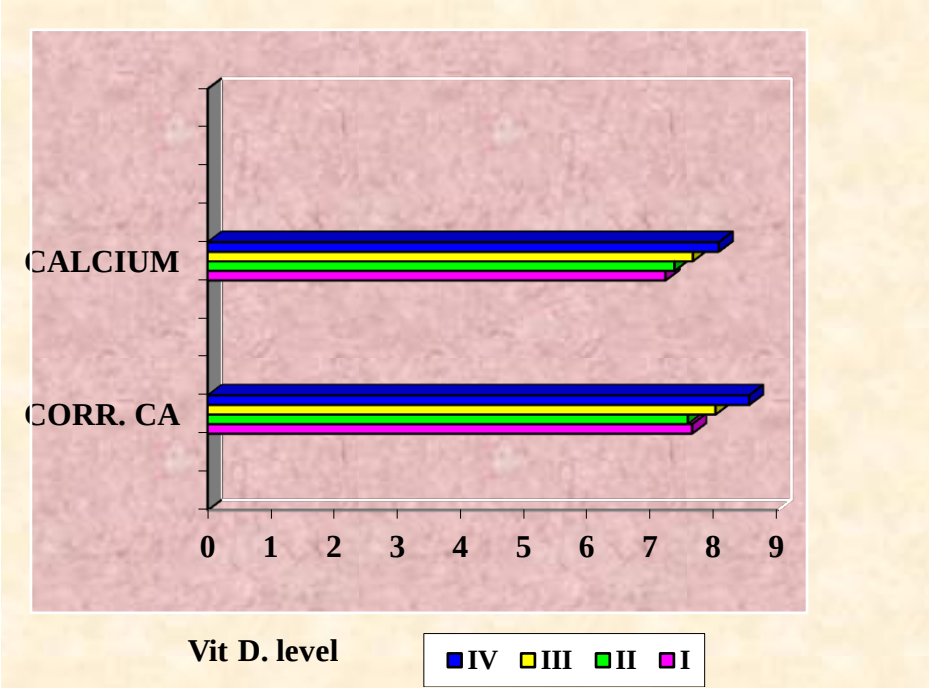


TABLE 11: VIT D LEVELS AND ECG CHANGES

Risk factors	**No. of cases with Vit D level**								**'p'**
	I		**II**		**III**		**IV**		
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
e) ECG									
LAD, LVH (23)	20	87	-	-	2	8.7	1	4.3	**0.0001**
WNL (17)	3	17.6	3	17.6	6	35.3	5	29.4	**Significant**

Percentage of ECG changes were significantly higher in cases with low vit D concentration (level I)

VITAMIN-D AND ECG CHANGE

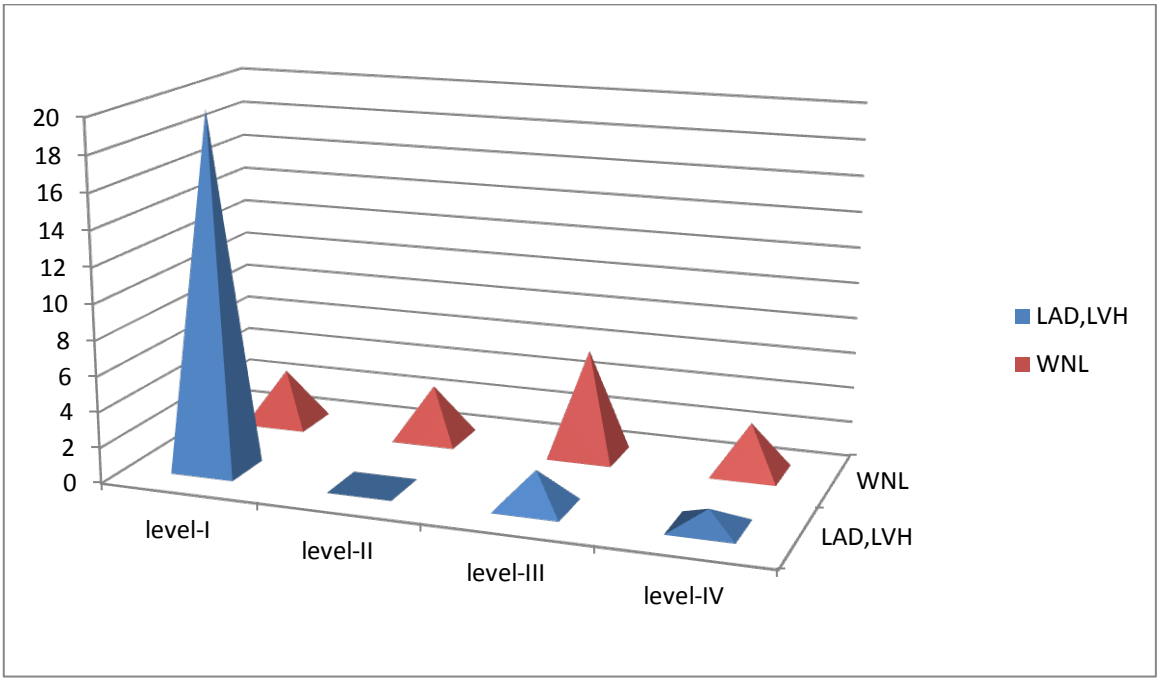


TABLE 12: VIT-D AND SMOKING

Risk factors	**No. of cases with Vit D level**								**'p'**
	I		**II**		**III**		**IV**		
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
a) Smoking among males									0.665
Yes (27)	16	59.3	2	7.4	5	18.5	4	14.8	Not
No (2)	1	50	-	-	1	50	-	-	significant

Smoking did not have any significant association in regard with vitamin-D levels.

TABLE 13: VIT-D AND CONCENTRIC LVH

Risk factors	**No. of cases with Vit D level**								**'p'**
	I		**II**		**III**		**IV**		
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
b) Echo									
Normal (21)	4	19	3	14.3	8	38.1	6	28.6	**0.0001**
Abnormal (19)	17	89.5	2	10.5	-	-		-	**Significant**

Percentage of abnormal echo were significantly higher in cases with low vit D concentration (level I)

VITAMIN-D AND LEFT VENTRICULAR HYPERTROPHY

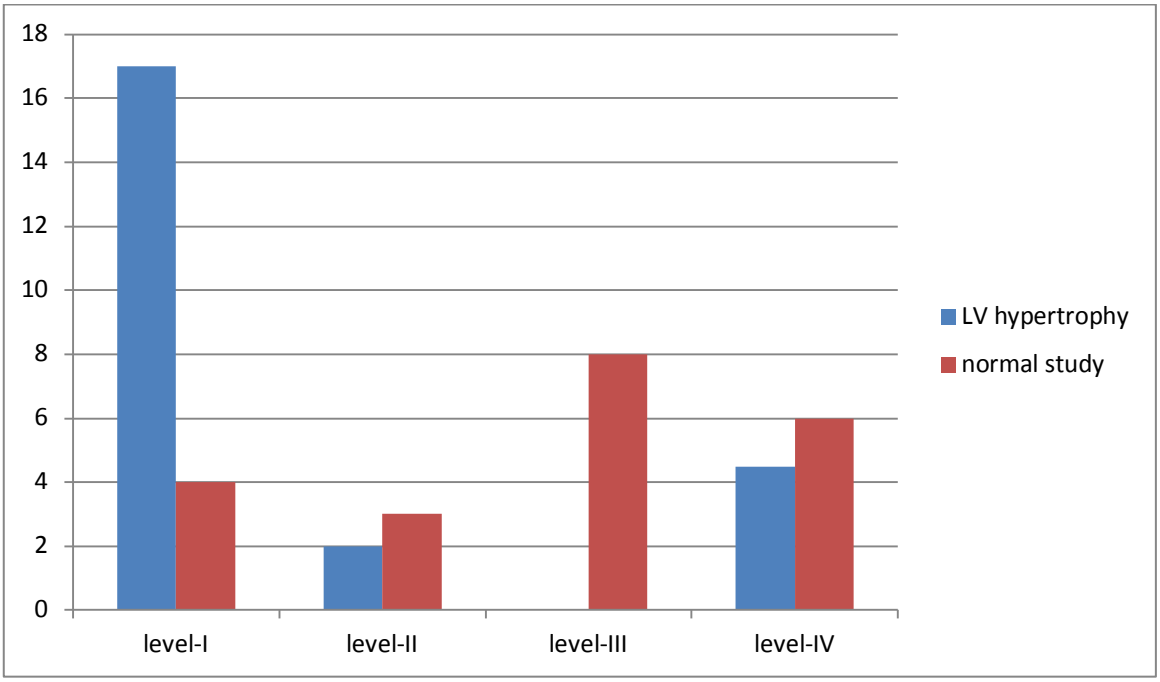


TABLE 14: VIT-D AND DM

Risk factors	**No. of cases with Vit d level**								**'p'**
	I		**II**		**III**		**IV**		
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
c) <u>DM</u>									
Yes (13)	11	84.6	-	-	2	15.4	-	-	**0.0389**
No (27)	12	44.4	3	11.1	6	22.2	6	22.2	**Significant**

Percentage of diabetic cases were significantly higher in cases with low levels of vitamin-D.

VITAMIN-D AND DIABETIC STATUS

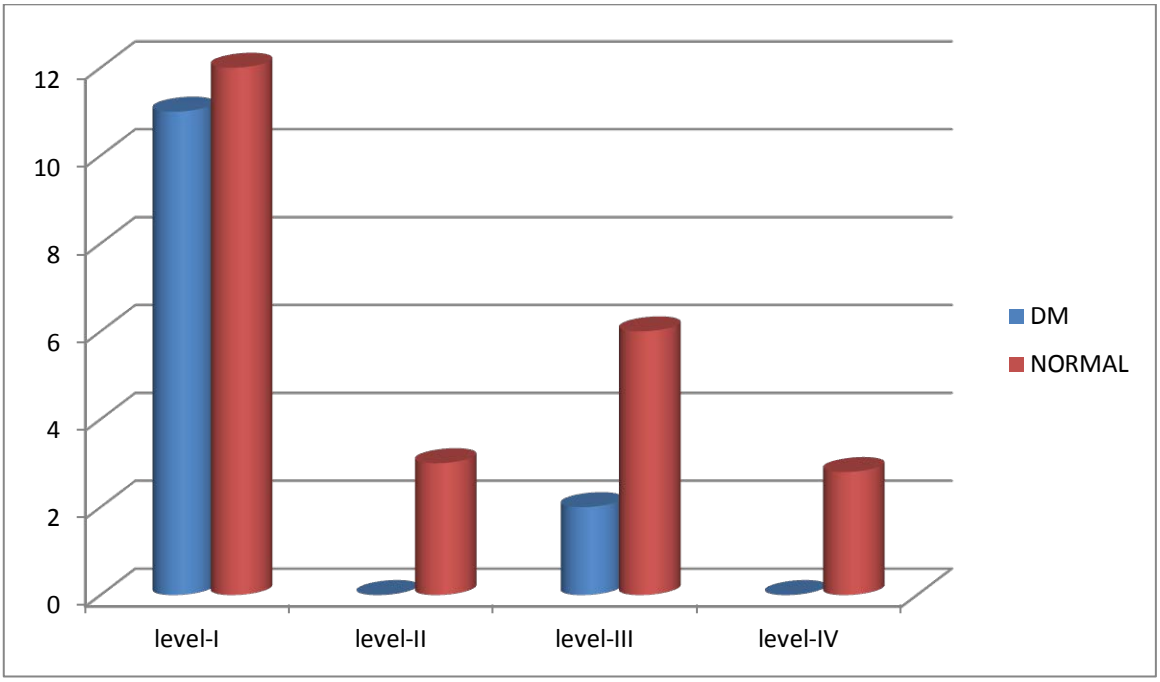
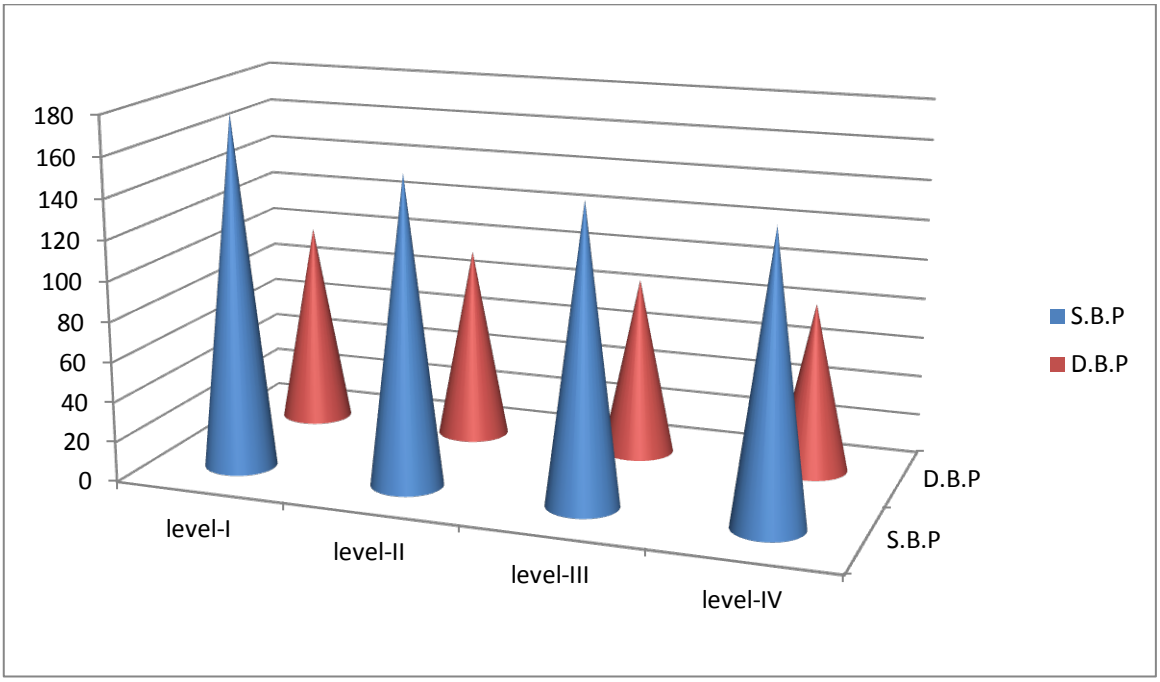


TABLE 15: VIT D LEVELS AND B.P

Vit D level	SBP		DBP	
	Mean	**SD**	**Mean**	**SD**
I	176.26	10.9	101.0	8.5
II	153.33	3.46	96	5.29
III	147	3.7	88.75	4.1
IV	142	2.5	84.33	4.8
'p'	0.0001 significant		0.0001 significant	

In the hypertensive cases, there was significant association between B.P values and vit D levels ($p < 0.05$).

VITAMIN-D AND BLOOD PRESSURE



DISCUSSION

Hypertension is one of the leading causes of morbidity and mortality in both developing and developed countries, which is usually found incidentally by healthcare professionals during a routine checkup[14].

Several potential mechanisms can explain the association of vitamin D deficiency with higher BP. Although the relationship between circulating levels of vitamin D and renin activity linkage was previously suggested in essential clinical hypertension studies[65] , it has just recently been demonstrated that 1.25(OH)2-D directly modulates the renin–angiotensin system [66]. Vitamin D deficiency is involved in secondary Hyperparathyroidism, and parathyroid hormone has been proved to have unfavourable cardiovascular effects, promoting arterial hypertension, left ventricular hypertrophy and cardiac fibrosis [67].

Other potential mechanisms could include the effects of vitamin D on the cells of the vessel wall, which include endothelial cells, vascular smooth muscle cells, and macrophages, all of which express the vitamin D receptor (VDR) as well as 1α-hydroxylase . Therefore an optimal level of circulating 1,25(OH)D which is regulated by 25(OH)D concentrations, is thought to be crucial for a normal level of BP . Our results are in line with these mechanisms and burgaz et al[68] indicate that men with vitamin D levels of <37.5 nmol/L have

a 3-fold increased risk for hypertension compared to men with normal levels (>75 nmol/L).

An inverse relationship between vitamin D and the renin angiotensin system (RAS) activity suggests that vitamin D may act as an endogenous inhibitor of the RAS . This association has also been observed in other studies[69,70.] (formann et al).

The authors of the Health Professionals Follow-Up Study of 38 388 men concluded that the 25(OH)D concentration required for normal BP was at least 37.5 nmol/L[71] (formann et al).An expert panel has recently recommended a target range for 25(OH)D concentrations of 75–100 nmol L) (30–40 ng mL) to reduce chronic disease including hypertension[72] (souberbille et al). In our study we included hypertensive patients and found out that their vitamin-D levels were definetly lower than the normotensive counterparts.

The first human study to investigate the association, that an inverse association existed between vitamin-D and hypertension examined 10 normotensive individuals, as well as 51 hypertensive individuals, on ambient diet and found out that all 61 individuals, there was an inverse correlation between PRA and 1,25(OH)2D (r__0.65; P_0.001)[73] (resnick et al). In our study around 85% of all hypertensive patients had vitamin –D level below the target

level (< 75nmol/L).one study by Jaume Almirall et al[74] showed 86% of the hypertensive patients had vitamin-D level less than 62.5nmol/L.

In this study age , sex , physical features like BMI were all adjusted between normotensive and hypertensive group. There was no confounding factor as suggested by the 'p' value. Both groups random blood sugar and renal functions were also matched .

However serum uric acid was found to be elevated in the hypertensive group as compared to normotensive patients .Similar results of elevated levels of uric acid in hypertensive patients is well documented[75] (cannon et al).

Likewise retinopathy, left ventricular hypertrophy on echocardiogram and electrocardiographic changes suggesting left axis deviation and left ventricular hypertrophy were seen in the hypertensive patients as compared to normotensive group.

The mean age in this study is 59. We have not included patients above the age of 70 as Aging decreases the amount of 7-dehydrocholesterol produced in the skin by as much as 75% by the age of 70 years. Therefore, a 70 year old person has approximately 25% of the capacity to produce cholecalciferol compared with a healthy young adult (Holick, *et al.* 1989)[76.]

We have divided the hypertensive group into four groups based on the vitamin-D level as level-I <37.5nmol/L, level –II 37.5nmol/l to

49.9nmol/L , level –III as 50nmol/L to 74.5nmol/L , and level-IV 75nmol/L to 100 nmol/L. This type of division is similar to that of a study conducted by burgaz et al[68] .

By dividing the patients into four groups we try to analyse whether any significance does really exists between decreasing level of vitamin-D and variables like systolic BP , diastolic BP, age , sex , BMI, serum calcium , retinopathy, left ventricular hypertrophy and electrocardiographic changes.

The mean vitamin-D level in male hypertensive was 45.7 and in females 49, which was statistically not significant. This is in contrast to study done by Ian H. de Boer et al in which they have shown that serum vitamin-D level was less in male subjects.

The serum vitamin-D level was significantly lower in hypertensive subjects when compared with normotensive patients. The mean vitamin-D level in cases was 46.6 and in controls was 62.3. Observational studies strongly support an inverse association between plasma 25(OH)D levels and blood pressure and hypertension[77] (Hintzpeter B).

The serum vitamin-D level was found to significantly associated with ECG changes like LAD, LVH and left ventricular hypertrophy. Two small clinical trials of hemodialysis patients have shown that treatment with activated vitamin D [1,25(OH)D or related analogs] may lead to regression of LVH,

suggesting a cardioprotective action [78,79] (park et al, kim et al) . Cardiac hypertrophy has been observed in the hearts of VDR knockout mice [80] (xiang et al). Activated vitamin D has been shown to downregulate proliferation and hypertrophy in cultured cardiomyocytes [81,82](wu et al , nibbelink et al).

In this study we found out the diabetic status of hypertensive patients and around 13 patients were found to have diabetes mellitus . we associated diabetes with various levels of vitamin-D , and found significant association. In a study done by Mathieu et[83] al they found out that Vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes, and receptors for its activated form-1alpha,25-dihydroxyvitamin D3-have been identified in both beta cells and immune cells.

No statistical significance was observed between vitamin –D level and smoking . The same was observed in the study conducted by Annamari Kilkkinen[84] et al were patients were classified based on their daily intake of nicotine level.

In our study we analysed systolic and diastolic blood pressure as continuous variable and compared with various levels of vitamin-D. There was a significant association between vitamin –D level and both systolic and

diastolic blood pressure. This is in line with the study conducted by Jaume Almirall et al[74] where the authors demonstrated significant association between vitamin-D and systolic and diastolic blood pressure. Also low 25(OH)-D levels were significantly and independently associated with a 6.6 mmHg increase in systolic BP (95% CI: 1.5–11.6) after controlling for the other variables in the study.

Vitamin-D deficiency has been documented to have elevated rennin level as Resnick et al[73] originally reported that plasma renin activity (PRA) and 1,25- dihydroxyvitamin D (1,25[OH]2D) were inversely correlated (*r*__0.65) among 61 individuals on an ambient diet. Several years later, Burgess et al[85] reported a similar association in 10 hypertensives (*r*__0.76). Interestingly, in a randomized trial that documented a 14-mm Hg decrease in SBP with vitamin D supplementation compared with placebo, the authors also noted a trend toward a decrease in circulating angiotensin II (Ang II) levels (_13.1 pg/mL; *P*_0.14) relative to placebo[86].

Not only does vitamin-D has a inverse relation with hypertension but studies by Harald Dobnig et al have showed Independent Association of Low Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Levels With All-Cause and Cardiovascular Mortality ,studies by Mark F. McCarty et al

showed that Poor vitamin D status may contribute to high risk for insulin resistance, obesity, and cardiovascular disease in Asian Indians.

Although many studies by burgaz et al and various other authors have demonstrated a inverse relation between vitamin-D and hypertension , few studies like the one by formann et al have demonstrated no significant association between vitamin-D level and hypertension. As there are controversies , it is suggested to carry out prospective studies among vitamin-D deficient patients and follow them to ascertain the rate of incident hypertension to ascertain the truth.

Conclusion :

- Hypovitaminosis D was found in 57.5% of hypertensive patients while only 10% of the normotensive subjects demonstrated low levels of vitamin-D.
- An inverse relation exists between vitamin-D and essential hypertension.
- Hypovitaminosis D was significantly associated with left ventricular hypertrophy.
- While considering systolic and diastolic blood pressure as continuous variables significant association was found with low levels of vitamin-D
- There is no correlation between serum vitamin-D level with age , gender, body mass index and smoking.

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GLOSSARY

UVB : ULTRAVIOLET B

25(OH)D : 25 HYDROXY VITAMIND

OCP : ORAL CONTRACEPTIVE PILL

NACL : SODIUM CHLORIDE

PRA : PLASMA RENNIN ACTIVITY

PAD :PERIPHERAL ARTERIAL DISEASE

CHF :CONGESTIVE HEART FAILURE

VDBP :VITAMIN D BINDING PROTEIN

VDR :VITAMIN D RECEPTOR

PTH :PARATHYROID HORMONE

MS :MULTIPLE SCLEROSIS

RA :RHEUMATOID ARTHRITIS

DM :DIABETES MELLITUS

IBD :INFLAMMATORY BOWEL DISEASE

CVD :CARDIOVASCULAR DISEASE

RAS :RENIN ANGIOTENSIN SYSTEM

CREB :C AMP RESPONSE ELEMENT BINDING PROTEIN

SD :STANDARD DEVIATION

SBP :SYSTOLIC BLOOD PRESSURE

DBP :DIASTOLIC BLOOD PRESSURE

ECG :ELECTROCARDIOGRAPHY

ECHO :ECHOCARDIOGRAM

CAD :CORONARY ARTERY DISEASE

LVH :LEFT VENTRICULAR HYPERTROPHY

BP :BLOOD PRESSURE

PROFORMA

NAME :	IP NO :
AGE/SEX : BMI:	WEIGHT: HEIGHT:

SMOKER:	PREVIOUS H/O OF CAD:
ALCOHOLIC:	HYPERTENSIVE:
POST MENOPAUSAL:	DIABETIC:

TREATMENT H/O:

General examination:

Vitals: pulse: BP: right left

Ul:

Ll:

Resp rate:

System examination:

Cvs:

Rs:

Abdomen:

Cns:

BLOOD INVESTIGATIONS:

UREA:

SUGAR:

CREATININE:

SERUM ELECTROLYTES:

SERUM PROTEINS:

SERUM VITAMIN D:

ECG :

Echo:

DIAGNOSIS:

TREATMENT:

S.No	AGE	SEX	HT	WT	BMI	SMO	S.B.P	D.B.P	UREA	SR.CR	CA	PHOSP	ALB	CORR.CA	ECG	ECHO	VIT-D	sr uric	retino	DM	RBS
1	31	M	1.58	60	24.035	Y	190	100	18	0.9	7.8	5	4.8	7.16	LAD,LVH	CONC.LVH	30.1	5.3	I	YES	218
2	61	M	1.59	70	27.689	Y	170	90	26	1	7.1	3.4	4	7.1	LAD,LVH	CONC.LVH	33.3	4.9	II	NO	88
3	55	F	1.48	59	26.936	N	160	100	34	1.2	7.1	3.3	3.2	7.74	LAD,LVH	CONC.LVH	32.8	6.2	NO	NO	110
4	68	M	1.62	70	26.673	Y	180	110	30	1.2	7.2	3.3	3.3	7.76	WNL	NORMAL	34.9	5.4	III	NO	124
5	42	M	1.64	69	25.654	Y	150	90	18	1.1	8.5	2.8	4	8.5	WNL	NORMAL	67.9	3.8	III	YES	98
6	61	M	1.65	70	25.712	N	170	90	32	1	7.9	3.9	3	8.7	LAD,LVH	CONC.LVH	28.2	8.6	IV	YES	135
7	63	M	1.66	78	28.306	Y	150	90	23	0.9	7.2	5	4	7.2	WNL	NORMAL	49.9	5.4	I	NO	154
8	56	M	1.75	67	21.878	Y	140	80	39	1.2	7.7	5.6	3.8	7.86	LAD,LVH	NORMAL	70	5.5	NO	NO	122
9	42	M	1.66	66	23.951	Y	140	90	18	1.3	8	4	3.5	8.4	WNL	NORMAL	88.5	4.8	III	NO	112
10	71	M	1.7	66	22.837	Y	150	90	23	1.2	7.6	3.7	3.4	8.08	WNL	NORMAL	50.5	6.9	I	NO	98
11	50	M	1.72	77	26.028	Y	170	100	42	1.9	7	2.8	3	7.8	LAD,LVH	CONC.LVH	29.2	8.1	IV	YES	256
12	65	M	1.74	70	23.121	y	200	120	24	1.1	7	4	3.5	7.4	LAD,LVH	CONC.LVH	31	6.8	III	YES	309
13	45	M	1.65	56	20.569	y	170	100	18	1	7	2.5	3.8	7.16	LAD,LVH	CONC.LVH	24.8	7.3	IV	NO	95
14	55	F	1.59	78	30.853	N	180	90	20	1.2	7.2	3.2	3.6	7.52	WNL	NORMAL	37.4	6.5	II	NO	93
15	60	F	1.55	67	27.888	N	150	90	26	1.3	7.6	4	3.2	8.24	WNL	NORMAL	68.9	5.2	I	NO	132
16	71	F	1.58	54	21.631	N	140	80	38	1.1	8.4	3.7	3	9.2	LAD	NORMAL	78.4	4.5	III	NO	116
17	65	M	1.66	68	24.677	Y	170	100	41	1.3	7.4	4	3.6	7.72	LAD	CONC.LVH	29.3	8.5	IV	YES	287
18	61	M	1.59	66	26.107	N	146	86	34	1.1	7.8	3	3.5	8.2	LAD,LVH	NORMAL	67.3	4.6	NO	NO	156
19	52	M	1.63	77	28.981	Y	144	88	27	1	8	4	3.5	8.4	WNL	NORMAL	79.8	3.3	NO	NO	133
20	74	M	1.58	56	22.432	Y	160	100	25	1.3	7.8	2.3	3.7	8.04	WNL	CONC.LVH	40.8	5.5	I	NO	129
21	56	M	1.61	78	30.091	Y	184	104	25	1	7.3	4.8	3.7	7.54	WNL	NORMAL	34.2	4.6	II	NO	132
22	65	M	1.64	78	29.001	Y	170	100	18	1.3	7.3	4.9	4	7.3	LAD,LVH	CONC.LVH	28.9	7.4	III	YES	243
23	50	M	1.58	66	26.438	Y	170	90	23	1.1	7.4	3.9	3.3	7.96	LAD,LVH	CONC.LVH	29.6	6.9	II	YES	254
24	61	F	1.54	55	23.191	N	160	100	21	1.2	7.7	4.5	3.2	8.34	LAD,LVH	NORMAL	34.4	4.4	IV	YES	265
25	66	F	1.51	59	25.876	N	146	88	31	1.2	7.1	3	3.3	7.66	WNL	NORMAL	78	5.4	NO	NO	122
26	60	F	1.58	64	25.637	N	190	110	30	1.1	7.2	4.1	3.5	7.6	LAD,LVH	CONC.LVH	31.2	6.9	NO	NO	77
27	42	F	1.54	59	24.878	N	150	94	34	1.4	7.3	3.8	3.8	7.46	WNL	NORMAL	59.6	5.4	NO	NO	85
28	60	M	1.61	66	25.462	Y	190	110	18	0.8	7	4.5	3.7	7.24	LAD,LVH	CONC.LVH	29.3	7.6	II	NO	94
29	61	M	1.62	76	28.959	Y	142	90	33	1	8.6	3.6	3.5	9	WNL	NORMAL	80	3.5	NO	NO	113

30	65	M	1.66	78	28.306	Y	180	100	28	1.2	7	4.5	3.9	7.08	LAD,LVH	CONC.LVH	20.8	7.3	IV	YES	214
31	50	F	1.58	70	28.04	N	170	90	34	1.4	7.1	3.7	3	7.9	LAD	CONC.LVH	33.5	5.9	III	YES	276
32	70	M	1.62	56	21.338	Y	140	80	31	1	7.4	4	3.1	8.12	WNL	NORMAL	72.9	6.4	I	NO	99
33	60	M	1.6	77	30.078	Y	170	110	32	1.5	7.1	3.8	3.2	7.74	LAD,LVH	NORMAL	34.3	7.5	II	YES	198
34	57	F	1.55	56	23.309	N	156	98	22	1	7.1	4.1	3.5	7.5	WNL	NORMAL	49.5	6.4	NO	NO	87
35	59	M	1.65	59	21.671	Y	180	110	32	1.2	7	4	3.4	7.48	LAD	NORMAL	32.5	5.9	NO	NO	98
36	67	M	1.66	54	19.596	Y	146	90	21	1	7.4	4	3.6	7.72	WNL	NORMAL	57.6	6.3	II	YES	213
37	56	F	1.56	51	20.957	N	170	100	23	1.5	7.7	3.2	3	8.5	LAD,LVH	CONC.LVH	34.9	7.4	II	NO	86
38	65	M	1.69	56	19.607	Y	144	90	27	1.2	8.3	2.8	3.6	8.62	WNL	NORMAL	88.9	3.9	IV	NO	73
39	77	M	1.65	59	21.671	Y	180	110	34	1.3	7.3	5.2	3.3	7.86	LAD,LVH	CONC.LVH	28.9	6.6	NO	NO	76
40	66	M	1.78	76	23.987	Y	160	90	33	1.2	7.1	4.9	3.7	7.34	LAD,LVH	CONC.LVH	30.5	5.4	NO	NO	94
41	56	M	1.69	78	27.31	N	130	80	32	1.1	8.2	3.8	3.5	8.6	WNL	NORMAL	73.4	3.5	NO	NO	88
42	67	M	1.7	67	23.183	Y	120	70	24	1.4	8.5	2.5	3.7	8.74	WNL	NORMAL	68.6	4.4	NO	NO	110
43	57	M	1.67	69	24.741	Y	110	70	32	1.3	7.9	2.8	3.6	8.22	WNL	NORMAL	59.9	3.9	NO	NO	109
44	60	M	1.59	70	27.689	N	120	80	29	1.3	7.8	3	3.5	8.2	WNL	NORMAL	69.3	3.6	NO	NO	75
45	59	M	1.67	79	28.327	Y	110	80	36	1.5	8.5	2.9	3.2	9.14	WNL	NORMAL	89.8	4.6	NO	NO	87
46	65	F	1.55	66	27.471	N	110	70	28	1.1	8.1	2.2	3.6	8.42	LAD	NORMAL	61.1	4.9	NO	NO	98
47	54	F	1.57	77	31.239	N	110	70	27	1.2	7.9	2.9	3.8	8.06	WNL	NORMAL	48.8	4.8	NO	YES	234
48	67	F	1.59	55	21.755	N	110	80	33	1.1	7.8	2.8	3.1	8.52	WNL	NORMAL	72.2	5.3	NO	NO	98
49	71	F	1.6	68	26.563	N	120	80	28	1.2	7.7	3.1	3.8	7.86	WNL	NORMAL	90	5.8	NO	NO	87
50	56	F	1.62	56	21.338	N	110	70	33	1.4	8.1	4.4	3.1	8.82	WNL	NORMAL	30.2	5.4	NO	YES	198
51	65	F	1.64	76	28.257	N	120	80	37	1.2	7.9	2.8	3.2	8.54	WNL	NORMAL	78.9	5	NO	NO	88
52	67	M	1.67	65	23.307	Y	110	70	28	1.5	8.1	3.6	3.7	8.34	WNL	NORMAL	39.9	4.7	NO	YES	254
53	69	M	1.71	67	22.913	Y	120	80	33	1.1	7.8	3.7	4	7.8	WNL	NORMAL	57.9	5.9	NO	NO	98
54	65	M	1.69	67	23.459	Y	110	80	31	1.3	8	2.9	3.2	8.64	WNL	NORMAL	70.2	4.3	NO	NO	78
55	70	M	1.76	87	28.086	Y	120	70	28	1.2	7.7	3.9	3.5	8.1	WNL	NORMAL	45.7	4.8	NO	YES	190
56	55	M	1.69	77	26.96	Y	110	70	33	1.2	8.5	2.5	3.1	9.22	WNL	NORMAL	69.8	5.4	NO	NO	98
57	65	M	1.76	65	20.984	Y	120	80	36	1.3	7.2	3.9	3	8	WNL	NORMAL	59	5.4	NO	NO	89
58	67	M	1.68	76	26.927	N	110	70	27	1.2	7.9	2.9	2.7	8.94	WNL	NORMAL	87	5.8	NO	NO	75
59	57	M	1.72	69	23.323	Y	120	70	28	1.8	8.1	3.9	4.1	8.02	WNL	NORMAL	49.9	4.3	NO	YES	178
60	67	M	1.67	71	25.458	Y	110	80	32	1.1	7.8	5	3.9	7.88	WNL	NORMAL	24.9	6.4	NO	YES	278